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10/627,331	07/25/2003	Arthur M. Krieg	C1039.70078US00	4362

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,331	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52,53,55-57,59,60,62-64,66-70 and 72-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,52,53,55-57,59,60,62-64,66-70 and 72-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/2004+07/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-49, 51, 54, 58, 61, 65, 71 and 87-96 are cancelled. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are pending and under examination.

Petition Decision

2. The petition filed July 12, 2007 has been **Granted**. The IDS filed January 14, 2004 has been considered, along with a clean copy of the 1449 submitted with the petition.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 recites a dependency to claim 58. However, claim 58 is a cancelled claim. Since claim 58 is a cancelled claim, it is unclear what is intended to be encompassed by claim 59. For the purpose of advancing examination, the Office will interpret that it is Applicant's intention to require claim 59 to recite a dependency to claim 57.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the written description rejection, Applicant argues that the written description requirement used by the office is incorrect. Rather than the statement provided by the Office, Applicant cited MPEP §2162, which actually states that:

"Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention."
In addition to above, Applicant submits that there is not requirement that Applicant demonstrate written description through actual reduction to practice or drawings.

Applicant's argument has been considered, however, contrary to Applicant's assertion, the written description standard used by the Office is proper and consistent with the text cited by Applicant. As noted previously, to provide adequate written description and evidence of possession, the specification must provide sufficient description of the claimed invention by i) actual reduction to practice, ii) reduction to drawings; or iii) disclosure of relevant identifying characteristics, such as disclosure of

complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention. Items i) and ii) are provided for by the statement "description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete," and item iii) is provided for by the statement "by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." Thus, contrary to Applicant's assertion, the written description standard applied by the Office is proper.

It should further be noted that while Applicant has cited MPEP § 2162 to contain the cited text, however, a difference in citation is noted. The cited text can be found in MPEP § 2163 rather than Applicant's cited MPEP § 2162.

Additionally, while it is not required that Applicant demonstrates written description through actual reduction to practice or drawings, however, had Applicant done so, Applicant would have satisfied the written description requirement. In this case, Applicant has not demonstrated possession of the claimed invention through actual reduction to practice or drawings. Of the three criteria used to determine possession of the claimed invention, it is noted that Applicant has failed to reasonably convey to the skilled artisan that Applicant is in possession of the claimed invention through actual reduction to practice and reduction to drawings.

With regard to the third criteria, it is noted that Applicant argues that Applicant has demonstrated adequate written description of the claimed invention through the

third criteria. Applicant argues that the description teaches of nucleic acid molecules that are useful with the claimed invention.

This argument has been considered, however, it is not found persuasive. In the instant case, the Office recognizes that the description teaches of numerous nucleic acid molecules. The Office has not denied the disclosure of this teaching. However, with regard to nucleic acid molecules that are therapeutically effective for HBV, the disclosure fails to teach any of such nucleic acid molecule. In the absence of such nucleic acid molecule, the skilled artisan would not be reasonably conveyed that Applicant is in possession of the claimed invention.

Additionally, it should further be noted that from a specification of about 68 pages, excluding the drawings, claims and abstract, the term "HBV" or "hepatitis B virus" is mentioned only ONCE. The term is mentioned in a laundry list of infectious virus that have been found in humans, which "include but are not limited to: Retroviridae (e.g. human immunodeficiency viruses, such as HIV-1 (also referred to as HTLV-III, LAV or HTLV-III/LAV, or HIV-III; and other isolates, such as HIV-LP; Picornaviridae (e.g. polio viruses, hepatitis A virus; enteroviruses, human Coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (e.g. strains that cause gastroenteritis); Togaviridae (e.g. equine encephalitis viruses, rubella viruses); Flaviridae (e.g. dengue viruses, encephalitis viruses, yellow fever viruses); Coronoviridae (e.g. coronaviruses); Rhabdoviradae (e.g. vesicular stomatitis viruses, rabies viruses); Coronaviridae (e.g. coronaviruses); Rhabdoviridae (e.g. vesicular stomatitis viruses, rabies viruses); Filoviridae (e.g. ebola viruses); Paramyxoviridae (e.g. parainfluenza viruses, mumps

virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (e.g. influenza viruses); Bungaviridae (e.g. Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); Arena viridae (hemorrhagic fever viruses); Reoviridae (e.g. reoviruses, orbiviurses and rotaviruses); Birnaviridae; Hepadnaviridae (**Hepatitis B virus**); Parvovirida (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV), herpes virus; Poxviridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (e.g. African swine fever virus); and unclassified viruses (e.g. the etiological agents of Spongiform encephalopathies, the agent of delta hepatitis (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1=internally transmitted; class 2=parenterally transmitted (i.e. Hepatitis C); Norwalk and related viruses, and astroviruses)." Besides this single instance, the specification does not further provide any additional description for hepatitis B virus. Due to the extremely limited description of hepatitis B virus, one of skilled in the art, reading the description, would not be reasonably convinced that Applicant was in possession of the claimed invention at the time it was filed. Overall, the description fails to reasonably convey to the skilled artisan that Applicant was in possession of the claimed invention at the time it was filed.

In response to the rejection, Applicant also argues that Applicant is not aware of a requirement for the specification to set forth "functional characteristics" of a compound in order to meet the written description requirement.

Applicant's argument has been considered, however, Applicant is advised to review MPEP § 2163, which clearly sets forth the use of functional characteristics a factor for determining if sufficient distinguishing characteristics is described in the specification.

As stated previously, the claimed invention is a method of treating, preventing or ameliorating a hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject.

The basic inquiry for possession is: Can one skilled in the art reasonably conclude that the inventor was in possession of the claimed invention at the time the application was filed? If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, *even if every nuance of the claim is not explicitly described in the specification*, then the requirement for an adequate written description is met.

To provide adequate written description and evidence of possession, the specification must provide sufficient description of the claimed invention by i) actual reduction to practice, ii) reduction to drawings; or iii) disclosure of relevant identifying characteristics, such as disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention. The analysis:

i) Sufficient description of the claimed invention by actual reduction to practice: Applicant admits on the record that Applicant has not demonstrated possession of the claimed invention by actual reduction to

practice. See page 10 of July 09, 2007 submission.

ii) Sufficient description of the claimed invention by reduction to drawings: Applicant admits on the record that Applicant has not demonstrated possession of the claimed invention by reduction to drawings. See page 10 of July 09, 2007 submission.

iii) disclosure of relevant identifying characteristics: Beside a lengthy description of nucleic acid molecules that have immunostimulatory activities, the disclosure does not contain a description of a single nucleic acid molecule that is therapeutically effective for HBV. In the absence of any evidence demonstrating that Applicant is in possession of the primary active ingredient for the claimed invention, oligonucleotides comprising the CpG motif that treat, prevents or ameliorate hepatitis B viral infection, the skilled artisan cannot reasonably be convinced that Applicant is in possession of the claimed invention at the time the invention was filed.

Furthermore, it should further be noted that from a specification of about 68 pages, excluding the drawings, claims and abstract, **the term "hepatitis B virus" is only mentioned once**, in a laundry list of other pathogenic viruses.

In summary, Applicant failed to reasonably convey to the skilled artisan, through actual reduction to practice, reduction to drawings, and disclosure of relevant identifying

characteristics, that Applicant was in possession of the claimed invention at the time it was filed.

Applicant is reminded that that written description requirement is separate and distinct from the enablement requirement.

7. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the enablement rejection, Applicant argues that the claimed invention is enabling. To support Applicant's arguments, Applicant argues that he specification contains working examples to show the production of antibody in response to oligonucleotide stimulation, stimulation of B cells, natural killer cells and monocytic cells, and production of IFN-gamma and other cytokines. [Examples 2-4, 11, Figures 6, 11 and 15.] Applicant notes that the specification asserts that CpG oligonucleotides are useful in treating viral infections including hepatitis B viral infection. Applicant further notes that Applicant has provided sufficient direction and guidance in the specification to enable the skilled artisan to practice the claimed invention. Applicant also notes that Applicant have provided preferred modes of administration and formulations. Applicant also disagrees with the Office position of unpredictability and quantity of experimentation necessary.

Applicant's arguments has been considered, however it is not found persuasive. The Office acknowledges the working examples disclosed in the specification. It is further noted that from this immunostimulatory observation, Applicant asserts that the oligonucleotides are useful in treating various diseases, including hepatitis B viral infection. However, as Applicant has noted, all that the Office has found is an "assertion" of use rather than any guidance or direction that would enable the skilled artisan to practice the claimed invention without the burden of undue experimentation. In the instant case, Applicant has not disclosed of a single oligonucleotide encompassed by the claimed invention to be therapeutically effective for HBV. Nor has Applicant sets forth an immune profile that the oligonucleotide must provide to render it therapeutically effective in HBV treatment. In the instant case, as noted by Applicant, all Applicant has taught is that the oligonucleotides are immunostimulatory. From this observation, Applicant associated the immunostimulatory activities to treating HBV. However, the association is not substantiated by any evidence demonstrating that the oligonucleotides are therapeutically effective for HBV. There is no in vitro nor in vivo model presented in the speciation to evidence that oligonucleotides encompassed by the claimed invention is therapeutic. In the instant case, Applicant has failed to set forth any guidance that would enable the skilled artisan to harness the observe immunostimulatory activity to render a therapeutically effective HBV treatment. As noted previously, nothing exists in the specification demonstrating that the fundamental research necessary for the claimed invention has been conducted to support Applicant's assertion of therapeutic efficacy for the oligonucleotides.

While it is noted that a portion of the specification is dedicated to modes of administration and preferred formulation, however, it should be noted that the enablement rejection is not directed at how to administer or formulate the oligonucleotides. The enablement rejection is directed at the failure of the specification to enable the skilled artisan to practice the claimed invention without the burden of undue experimentation. In the instant case, as noted above, Applicant has not evidence that an oligonucleotide is therapeutically effective in HBV treatment.

It is further noted that Applicant objected to the Office conclusion that all that is present in the specification are conjectures of potential application of such oligonucleotides against viral infection, and requested the Office to substantiate this position.

Applicant's objection has been noted, however, the Office stands by this position. In this case, Applicant has not shown or taught that an oligonucleotide comprising the CpG motif has a therapeutic affect against viral infection. All that Applicant has shown is that these oligonucleotides are immunostimulatory, and from these immunostimulatory activities, Applicant asserts that they are useful in the treatment of viral infections. Applicant has not substantiated this assertion by any facts that correlates and commensurate with the claimed invention. As mentioned, the claimed invention is specifically directed at treating, preventing and ameliorating HBV infection. However, Applicant has not taught or provided any guidance directing at the type of immunoparameter that must be modulated, which oligonucleotide has this immunomodulatory activity, and the extent in which the modulation must occur to render

a therapeutic effect against HBV infection. All that is present is an assertion of use without any substantiating evidence. Similarly, all that is present are conjectures, reasoning that involve the formation of conclusions from incomplete evidence, of use.

Applicant further submits that much of the art cited in the enablement are not relevant to the current claimed invention. Applicant also asserts that there is no evidence of unpredictability of the invention.

Applicant's submission has been considered, however, it is not found persuasive. It should be noted that the claimed invention is directed at the treatment of HBV infection with the administration of a CpG oligonucleotide. The claimed invention is directed at the administration of CpG oligonucleotides to stimulate a Th1 immune response, which induces the production of Th1 associated cytokines. In the instant case, while the claimed invention does not specifically recites the administration of a cytokine, it does relies on the production of a Th1 associated cytokines to render a therapeutic efficacy for a disease. Hence, the cytokine art was introduced in the enablement rejection to demonstrate the level of unpredictability and the quantity of experimentation that would be required of the skilled artisan attempting to practice the claimed invention. In the instant case, the Office relies on the cytokine art to establish that the skilled artisan would not be able to practice the claimed invention without an undue burden of experimentation.

Additionally, these post-filing art evidences that a method of treating HBV with the administration of an oligonucleotide comprising the CpG motif has not been ascertained by any skilled artisan in the relevant art.

It is further noted that Applicant criticized the Office for citing teachings of the cytokine art. Applicant argues that it is not clear how the teachings are relevant to the claimed invention, which is directed at method of treatment for HBV with the administration of oligonucleotides.

Applicant's criticisms have been noted, however, because Applicant has disclosed in the specification that the claimed invention relies on the immunostimulatory activities of oligonucleotides comprising CpG motifs to treat HBV. Specifically, Applicant disclosure suggests taking advantage of the Th1 biased immune response induced by the oligonucleotides to treat HBV. In association with a Th1 immune response is the induction of Th1 associated cytokine profiles. The induction of Th1 associated cytokines necessarily follows the production of a Th1 immune response. Hence, the Office cited the teachings of the cytokine arts. These teachings demonstrated that the direct administration of cytokines itself is unpredictable. Hence, if the direct administration of cytokines is unpredictable, it logically follows that the indirect administration of cytokines, via stimulation of a Th1 biased immune response, would necessarily be unpredictable, if not more unpredictable.

In addition to above, Applicant criticizes the Office's interpretation of Krieg and Mutwiri et al. Applicant argues that Office conclusion that the absence of TLR9 in some species would lead to variability in results is misplace, and notes that Mutwiri et al. discloses that in vitro stimulation of cells by CpG motifs is conserved across species. In response to the Office position that every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation

induced by these oligonucleotides varies...etc.," Applicant argues that Applicant has described a class of oligonucleotides comprising the CpG motif that favors a Th1 immune response, and that variability in the immune response induced by the oligonucleotides should not be the cause for a lack of enablement. Applicant further argues that the statement that the "immunostimulatory activity of CpG oligonucleotides is species specific," does not support a lack of enablement.

Applicant's position has been carefully considered, however, it is not found persuasive. It should be noted that the enablement rejection is not based solely on the species specific immunostimulatory activities nor the variability of the immune response induced by oligonucleotides comprising the CpG motifs. The enablement rejection is made on the basis of the Wands factors. A conclusion of lack of enablement means that claimed subject matter was not described in the specification, in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to use the invention. In this case, the two cited points are directed at the lack of predictability present in the CpG art. The CpG art clearly notes that immunostimulatory activities vary from one species to the next. That is the immunostimulatory activities observed in mice would not necessarily be predictive of the immunostimulatory activities in humans. The CpG art also clearly cautions that the immune response in each oligonucleotide comprising the CpG motif is distinct from one another. That is, while Applicant has alleged that Applicant has disclosed a class of oligonucleotides that produces a Th1 biased immune response, however, as noted above, the Th1 associated cytokine profile induced by these oligonucleotides is distinct

from one another. The existence of variability in the Th1 associated cytokine profile induced by each oligonucleotides comprising the CpG motif, depending on the length of the sequence, the sequences that flanks the CpG motif, the number of CpG motifs...etc., would not enable the skilled artisan to predictably and routinely pick any oligonucleotide comprising the CpG motif, as encompassed by the claims, to treat HBV. Additionally, it is noted that Applicant has alleged that the Office' conclusion that the absence of TLR9 in some species would lead to variability in results is misplace because Mutwiri et al. discloses that in vitro stimulation of cells by CpG motifs is conserved across species. It appears that Applicant has misconstrued the Office's conclusion. As noted in the previous office action:

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines.[1] However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice.[2] Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next.

The conclusion noted by the Office is the level of Th1 immune response is also dependent on TLR-9 expression, which varies from one species to the next. Moreover,

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[1] Krieg et al. CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [Abstract, in particular.]

the Office directs Applicant's attention to Krieg et al.[3] Krieg et al. clearly notes that because the cellular patterns of TLR expression varies between different species, the results of TLR stimulation in one species may not be predictive of what will occur in another. The disclosure of Krieg et al. clearly substantiates the Office's conclusion.

Thus, while all of Applicant's arguments and criticisms have been carefully considered, the entire submission is not sufficient to over come the enablement rejection. In this case, Applicant has failed to evidence that the claimed subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

In all, Applicant is reminded that the enablement rejection is made on the basis of the Wands factors. In view of the Wands factors, as established in the previous office action, it is found that the specification is not enabling for the claimed invention. While Applicant may argue that the specification is enabling, the evidence as a whole evidences that Applicant has enabled the skilled artisan to practice the claimed invention without undue experimentation. Applicant has not provided a single working example that is directed at demonstrating at an oligonucleotide comprising the CpG motif is therapeutic against HBV infection, nor any guidance evidencing that said oligonucleotide is indeed therapeutic against HBV infection. This is further exemplified by Applicant's submission, wherein Applicant repeatedly asserted that Applicant teaches the use of the oligonucleotide to induce an immune response. And, Applicant

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[2] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93.]

is reminded that this teaching does not commensurate in scope with the claimed invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the claims:

The claimed method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject.

The specification provides the following,

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[3] Krieg et al. Antiinfective Applications of Toll-Like Receptor 9 Agonists. Proc. Am. Thorac. Soc., Vol. 4, 2007, 289-294.

A "subject" shall mean a human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse. [Lines 31-32, page 19.]

Hence, the breadth of the claims is directed to a method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject. The subjects encompassed by the claimed invention are all vertebrate animals, including humans.

Presence or Absence of working examples:

The specification does not contain any working examples that are directed to the claimed invention, a method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising the CpG motif. The specification does not containing any working examples demonstrating that such oligonucleotides treat, prevent or ameliorate hepatitis B viral infection. Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicant's claim, wherein oligonucleotides comprising the CpG motif treat, prevent or ameliorate hepatitis B viral infection in vertebrate subjects.

Amount of direction or guidance present in the specification:

The specification does not contain any evidence demonstrating that oligonucleotides containing the CpG motif treat, prevent or ameliorate hepatitis B viral infection in vertebrate subjects. All that is present in the specification are conjectures of potential application of such oligonucleotides in the treatment, prevention and amelioration of viral infections in vertebrate subjects.

Nature of the invention

Based on Applicant's disclosure, it appears that the nature of the claimed invention is directed to the use of the immunostimulatory activity of oligonucleotides containing the CpG motif, including the induction of Th1 immune response invoked by the production of Th1 associated cytokines accorded by the CpG motif to render a therapeutic value, wherein the desired therapeutic value is to provide treatment, prevention and amelioration of hepatitis B viral infection in vertebrate subject--immunotherapy.

State of the Art:

In the instant, the involvement of a Th1 type immune response in combating against intracellular pathogens is a well-recognized general concept. The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Th1-associated cytokine to the treatment, prevention and amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious diseases, the production of the "right" set of cytokines can be a matter of life or death, as noted by Infante-Duarte et al. Infante-Duarte et al. further notes that in addition to a Th1 type immune response, a Th2 type immune response is also necessary. Specifically, Infante-Duarte et al. teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the

Th1 type immune response from causing damage to the host.[4] Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection.

The cytokine art also provides that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12 and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al.,[5] Bohn et al.,[6] Sakao et al.,[7] Zaitseva et al.,[8] and Masihi, K.[9] Aoki et al. teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection. Bohn et al. teaches that interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice. Sakao et al. teaches that interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. Zaitseva et al. teaches that both interleukin 6 and interferon gamma

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[4] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[5] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[6] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]
[7] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[8] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]

augment the susceptibility of monocyte-derived macrophages to infection. Masihi, K. notes that interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. In summation, the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated.

Additionally, while the art teaches that oligonucleotides containing the CpG motif are capable of stimulating a Th1 type immune response, however, the art also teaches that the Th1 associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next, as evidenced by Krieg et al. [10] and Mutwiri et al. [11] Krieg et al notes that each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Krieg et al. particularly notes that the type of cytokine stimulated by oligonucleotides containing the CpG motif is distinct from one oligonucleotide to the next. Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacings between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the

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[9] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]

[10] Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [paragraph that bridge pages 716-717, in particular.]

[11] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90.]

absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence.

The CpG art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically, Mutwiri et al. notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.

Furthermore, both Krieg et al. and Mutwiri et al. sets forth that the recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al. provides that TLR-9 has only been identified in mice and humans. Mutwiri et al. also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9, then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one species to the next. Mutwiri et al. also sets forth that *in vitro* observations do not accurately predict what happens *in vivo*.

Moreover, the potential use of oligonucleotides containing the CpG motif to stimulate a Th1 type immune response that treats and prevents infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive, as evidenced by Yamamoto et al., [12] Equils et al.,[13] Agrawal et al.,[14] and Olbrich et al.[15] Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza. Equils et al. teaches that such oligonucleotides can induce the HIV transcriptional regulatory elements in long terminal repeats, increasing viral replication. Agrawal et al. teaches that HIV-infected humans treated with oligonucleotides containing the CpG motif showed dose-dependent increases viral load. Lastly, Olbrich et al. teaches that the administration of oligonucleotides containing the CpG motif accelerated and increased the severity of Friend retrovirus in mice. In the case of Olbrich et al., the author notes that the use of oligonucleotides containing the CpG motif for the treatment of viral infection may be a double edge sword that can resolute in effective therapy but also in acceleration of disease. Olbrich et al. notes that this double edge sword observation may be dependent on the time point of treatment.

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[12] Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40.
[13] Equils et al. Toll-like receptor 2 (TLR2) and TLR9 signaling resulted from HIV-long terminal repeat transactivation and HIV replication in HIV-1 transgenic mouse spleen cells: implications of simultaneous activation of TLRs on HIV replication. J. Immunol. 2003, 170, 5159-5164.
[14] Agrawal, et al. Was induction of HIV1 through TLR9? J. Immunol. 2003, 171, 1621-1621.
[15] Olbrich et al. Preinfection treatment of resistant mice with CpG oligodeoxynucleotides renders them susceptible to friend retrovirus-induced leukemia. J. Virol., 2003, 77, 10658-10662.

Hence, overall, the literature notes the use of CpG to stimulate the production of cytokines, the use of cytokines to influence viral infection, and the development of a treatment regimen for diseases is unpredictable and complicated.

Predictability or unpredictability of the art:

As discussed above, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. The art also recognizes that use of CpG to stimulate cytokine production, the use of the induced cytokine to influence viral infection, and the development of treatment regimen unpredictable and complicated. The art additionally teaches that the efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protects a host from infectious pathogen has proven to be challenging and elusive.

Quantity of experimentation necessary:

Extreme undue burden of experimentation would be imposed upon the skilled artisan practicing the claimed invention. As stated above, Applicant has not provided much, if any, guidance or direction relating to the claimed invention. All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that CpG oligonucleotides are capable of inducing a biased Th1 immune response, and that Th1 immune response are useful in treating infections. And the formation of a conclusion based on generalized concepts renders the conclusion flawed. Generalized concepts are directed to support a general direction of studies or research; however, they do not support concrete conclusions, the use of oligonucleotides to treat HBV. Concrete conclusions must be substantiated by facts, including evidence. In the instant

case, while the general direction of research may be outlined for the skilled artisan, the skilled artisan would not readily be able to practice the claimed invention without the burden of undue experimentation. The path the skilled artisan must take in his research is marked with many challenges that are recognized in the art, including the complex nature of oligonucleotides containing CpG motif and the complexity of the immune system, including the Th1 type immune response and the functional characteristics of its associated cytokines. Hence, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat, prevent or ameliorate viral infection in a subject; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan would not be able to reasonably practice the claimed invention without an undue burden experimentation. Thus, the claims are rejected under 35 U.S.C § 112, 1st paragraph for failing to comply with the enablement requirement.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. In response to the provisional double patenting rejection, Applicant has deferred substantive rebuttal until the claimed invention is allowed.

Applicant's request has been noted, however, until the rejections are properly addressed, the rejections are maintained.

10. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 59-61, of copending Application No. 11/255100.

The claimed invention is directed to a method of treating, preventing and ameliorating hepatitis B viral infection with the administration of an oligonucleotide comprising the CpG motif.

Claims 59-61 of the conflicting patent application is directed to a method of treating hepatitis B viral infection with the administration of an oligonucleotide comprising the CpG motif, SEQ ID NO: 27, to a subject having or at risk of HBV infection.

The difference between the claims is: claims 59-61 of the conflicting patent application is directed to the administration of a specific oligonucleotide. However, the claimed invention recites the transitional term "comprising". Hence, the claimed invention also encompasses the species of oligonucleotides recited in the claims of the conflicting patent application. In the instant, the species of oligonucleotides recited in claims 59-61 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Thus, the species of oligonucleotides recited in claims 59-61 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 40 and 97 of copending Application No. 10/613524. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claim 97 of the conflicting patent application is directed at a method for preventing disease in a subject with the administration of an oligonucleotide comprising the CpG motif, wherein the oligonucleotide has the sequence of SEQ ID NO:1.

The difference between the claim sets is: Claim 97 of the conflicting patent application is limited to the administration of a specific oligonucleotide. However, the claimed invention recites the transitional term "comprising". Hence, the claimed invention also encompasses the species of oligonucleotides recited in the claims of the conflicting patent application. In the instant, the species of oligonucleotides recited the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Thus, the species of oligonucleotides recited the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

The other difference noted between the claim sets is: Claim 97 of the conflicting patent application is non-specific as to the type of diseases intended. However, it is noted that claim 40 of the conflicting patent application suggests the administration of

SEQ ID NO: 1 to treat and prevent an infectious disease. To further understand the type of disease(s) intended by the claim, the Office looked to the specification. It is noted that the specification lists hepatitis B virus infection as a disease intended by Applicant. [Paragraph [0022] of the application's PreGrant publication] Hence, in the instant, the conflicting patent application is also directed at a method of treating and preventing hepatitis B viral infection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-33, of copending Application No. 10/987146.

Claims 19-33 of the conflicting patent application is directed at a method for treating viral infection with the administration of an oligonucleotide comprising the CpG motif to said subject.

The difference between the claim sets is: the conflicting patent application is not limiting to the type of viral infection it intends to treat. However, in view of the disclosure of the conflicting patent application, by viral infection, Applicant intends to encompass hepatitis B viral infections. See line 19, page 13 of the conflicting patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70 and 72-86 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being

unpatentable over claims 47, 52, 57, 72 and 74, of copending Application No. 11/071836.

Claims 47, 52, 57, 72 and 74 of the conflicting patent application is directed at a method for treating viral infection with the administration of an oligonucleotide comprising the CpG motif to said subject, wherein the oligonucleotide has the sequence of SEQ ID NO: 46.

The difference between the claim sets is: the conflicting patent application requires the oligonucleotide to comprise SEQ ID NO: 46, whereas, the claimed invention is not limiting to a particular sequence. However, the claimed invention recites the transitional term "comprising". Hence, the claimed invention also encompasses the species of oligonucleotides recited in the claims of the conflicting patent application. In the instant, the species of oligonucleotides recited in the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Thus, the species of oligonucleotides recited the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Note: Some of the rejections stated above, in part, based on the specification of a previously issued patent, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II(B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of

the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.

The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

Conclusion

14. No claims are allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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